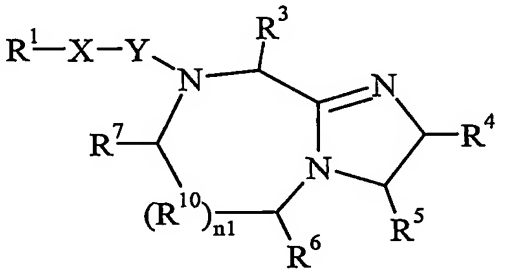
CLAIMS

1. A pharmaceutical composition comprising a farnesyl transferase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said farnesyl transferase inhibitor or of said farnesyl transferase inhibitor prodrug, and an anthracycline, a prodrug thereof or a pharmaceutically acceptable salt of said anthracycline or of said anthracycline prodrug.

2. A pharmaceutical composition according to claim 1, wherein said farnesyl transferase inhibitor is according to formula I:



(I)

wherein

n1 is 0 or 1;

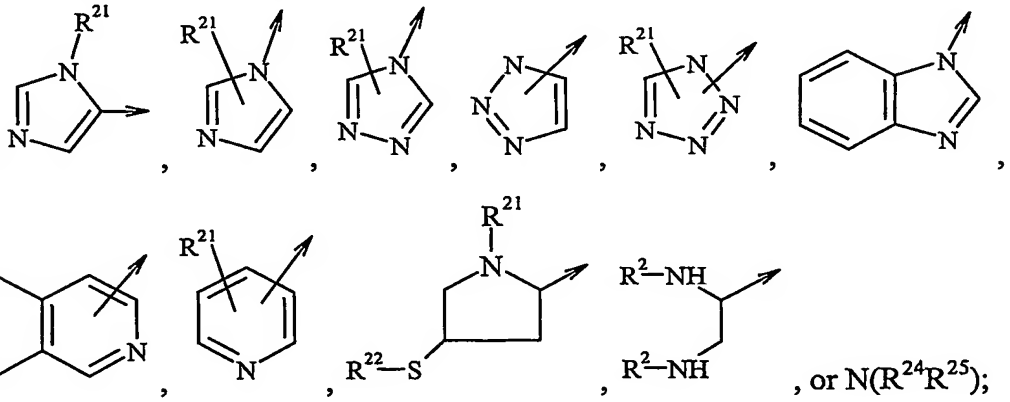
X is, independently for each occurrence, $(CHR^{11})_{n3}(CH_2)_{n4}Z(CH_2)_{n5}$;

Z is O, $N(R^{12})$, S, or a bond;

n3 is, independently for each occurrence, 0 or 1;

n4 and n5 each is, independently for each occurrence, 0, 1, 2, or 3;

Y is, independently for each occurrence, CO, CH_2, CS, or a bond;

R^1 is 

R^2 , R^{11}, and R^{12} each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl, wherein said optionally substituted moiety is optionally substituted with one or more of R^8 or R^{30};

R^3 is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30};

R^4 and R^5 each is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, aryl, and heterocyclyl, wherein said optionally substituted moiety is optionally substituted with one or more R^{30}, wherein each said substituent is independently selected, or R^4 and R^5 can be taken together with the carbons to which they are attached to form aryl;

R^6 is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, $-N(R^8R^9)$, -COOH, $-CON(R^8R^9)$, and halo,
where R^8 and R^9 each is, independently for each occurrence, H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{2-6})alkynyl, aryl, or aryl(C_{1-6})alkyl;

R^7 is, independently for each occurrence, H, =O, =S, or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-6})alkyl, (C_{5-7})cycloalkenyl, (C_{5-7})cycloalkenyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, heterocyclyl, and heterocyclyl(C_{1-6})alkyl, wherein said optionally substituted moiety is

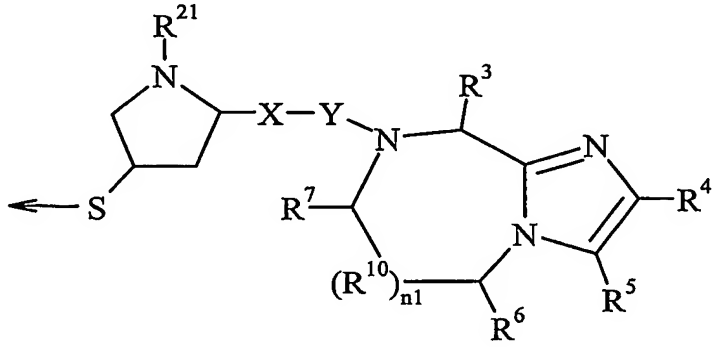
optionally substituted with one or more substituents each independently selected from the group consisting of OH, (C_{1-6})alkyl, (C_{1-6})alkoxy, $-N(R^8R^9)$, -COOH, $-CON(R^8R^9)$, and halo;

R^{10} is C;

or when n1 = 0, R^6 and R^7 can be taken together with the carbon atoms to which they are attached to form aryl or cyclohexyl;

R^{21} is, independently for each occurrence, H or an optionally substituted moiety selected from the group consisting of (C_{1-6})alkyl and aryl(C_{1-6})alkyl, wherein said optionally substituted moiety is optionally substituted with one or more substituents each independently selected from the group consisting of R^8 and R^{30};

R^{22} is H, (C_{1-6})alkylthio, (C_{3-6})cycloalkylthio, R^8–CO-, or a substituent according to the formula



;

R^{24} and R^{25} each is, independently for each occurrence, H, (C_{1-6})alkyl, or aryl(C_{1-6})alkyl;

R^{30} is, independently for each occurrence, (C_{1-6})alkyl, $-O-R^8$, $-S(O)_{n6}R^8$, $-S(O)_{n7}N(R^8R^9)$,

$-N(R^8R^9)$, -CN, $-NO_2$, $-CO_2R^8$, $-CON(R^8R^9)$, $-NCO-R^8$, or halogen;

n6 and n7 each is, independently for each occurrence, 0, 1, or 2;

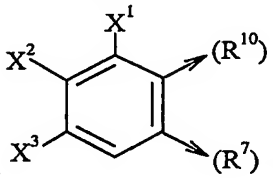
wherein said heterocyclyl is azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl,

morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, or thienyl; and

wherein said aryl is phenyl or naphthyl;

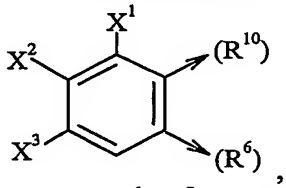
provided that:

when n1 = 1, R^{10} is C and R^6 is H, then R^{10} and R^7 can be taken together to form



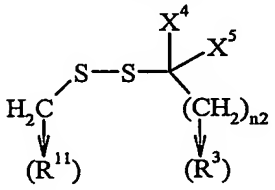
; or

when n1 = 1, R^{10} is C, and R^7 is =O, -H, or =S, then R^{10} and R^6 can be taken together to form



wherein X^1, X^2, and X^3 each is, independently, H, halogen, $-NO_2$, $-NCO-R^8$, $-CO_2R^8$, -CN, or $-CON(R^8R^9)$; and

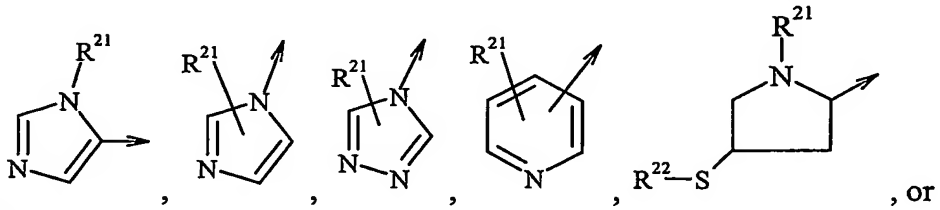
when R^1 is $N(R^{24}R^{25})$, then n3 is 1, n4 and n5 each is 0, Z is a bond, and R^3 and R^{11} can be taken together to form



wherein n2 is 1-6, and X^4 and X^5 each is, independently, H, (C_{1-6})alkyl, or aryl, or X^4 and X^5 can be taken together to form (C_{3-6})cycloalkyl;

or a pharmaceutically acceptable salt thereof.

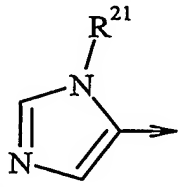
3. A pharmaceutical composition according to claim 2, wherein:

R^1 is  , or $N(R^{24}R^{25})$; and

X is $CH(R^{11})_{n3}(CH_2)_{n4}$ or Z, wherein when X is Z, Z is O, S, or $N(R^{12})$;

or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition according to claim 3, wherein:

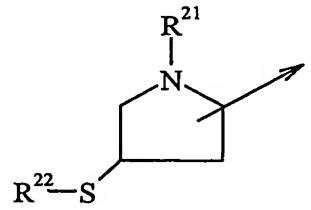
R^1 is  ;

X is $CH(R^{11})_{n3}(CH_2)_{n4}$; and

n1 is 0;

or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition according to claim 3, wherein:

R^1 is  ;

n3, n4, and n5 each is 0;

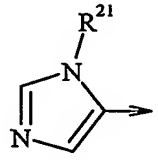
Z is a bond;

Y is, independently for each occurrence, CO or CS; and

n1 is 0;

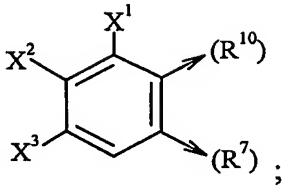
or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition according to claim 3, wherein:

R^1 is  ;

R^6 is H;

n1 is 1;

R^7 and R^{10} are taken together to form  ;

n3 is 1 and R^{11} is H;

Z is O or a bond;

n5 is 0; and

Y is CO, CH_2, or a bond;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 3, wherein:

R^1 is $N(R^{24}R^{25})$;

n1 is 0;

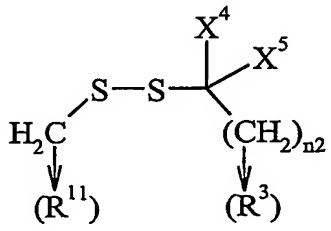
n3 is 1;

n4 is 0;

n5 is 0;

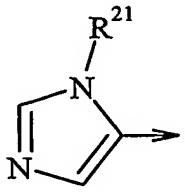
Y is CO or CS;

Z is a bond; and

R^3 and R^{11} are taken together to form  ,

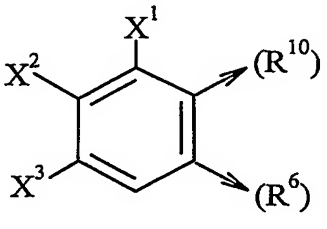
or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 3, wherein said farnesyl transferase inhibitor is a compound of formula I, wherein:

R^1 is  ;

R^7 is H or =O;

n1 is 1;

R^6 and R^{10} are taken together to form  ;

n3 is 1 and R^{11} is H;

n5 is 0;

Y is CO or CH_2; and

Z is O or a bond;

or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition according to claim 2, wherein said farnesyl transferase inhibitor is:

8-butyl-7-(3-(imidazol-5-yl)-1-oxopropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

8-butyl-2-(2-hydroxyphenyl)-7-(imidazol-4-yl-propyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

8-butyl-7-(4-imidazolylpropyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-(imidazol-4-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

2-(2-methoxyphenyl)-8-(1-methylpropyl)-7-(1-oxo-2-(1-(phenylmethyl)-imidazol-5-yl)ethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

2-(2-methoxyphenyl)-8-(1-methylpropyl)-7-(2-(1-phenylmethyl)-imidazol-5-yl)ethyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-(1-(4-cyanophenylmethyl)-imidazol-5-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-((1H-imidazol-4-yl)methyl)-2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-((4-imidazolyl)carbonyl)-2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(1-(4-cyanophenylmethyl)-imidazol-5-yl)methyl-2-(2-methoxyphenyl)-8-(1-methylpropyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-(4-cyanophenylmethyl)-imidazol-5-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine;

5-butyl-7-(2-(4-cyanophenylmethylimidazol-5-yl)-1-oxo-ethyl)-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

6-butyl-7-(2-(4-cyanophenylmethylimidazol-5-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine;

6-butyl-7-(2-(4-cyanophenylmethylimidazol-5-yl)-1-oxo-ethyl)-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine;

5-butyl-7-(2-(1-(4-cyanophenylmethyl)-imidazole-5-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-(1-(4-cyanophenylmethyl)-imidazole-5-yl)-1-oxo-ethyl)-8-(cyclohexylmethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

5-butyl-7-(2-(1H-imidazole-5-yl)-1-oxo-ethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine;

7-(2-(4-cyanophenylmethyl)-imidazol-5-yl)-1-oxo-ethyl)-2-(2-(phenylmethoxy)-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine; or

2-(2-butoxyphenyl)-7-(2-(4-cyanophenylmethyl)-imidazol-5-yl)-1-oxo-ethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition according to claim 2, wherein said farnesyl transferase inhibitor is:

1,2-dihydro-1-((1H-imidazol-4-yl)methyl)-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine ;

9-bromo-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

9-Chloro-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

10-Bromo-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-8-fluoro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine; or
or a pharmaceutically acceptable salt thereof.

11. A combination according to claim 10, wherein said farnesyl transferase inhibitor is:

1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine ;

9-bromo-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

9-Chloro-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

10-Bromo-1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

1-(2-(1-(4-cyanophenylmethyl)imidazol-4-yl)-1-oxoethyl)-1,2-dihydro-8-fluoro-4-(2-methoxyphenyl)-imidazo[1,2-c][1,4]benzodiazepine;

12. A combination according to claim 2, wherein said farnesyl transferase inhibitor is:

7-(2-amino-1-oxo-3-thiopropyl)-8-(mercaptoethyl)-2-(2-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2a]pyrazine disulfide;
or a pharmaceutically acceptable salt thereof.

13. A combination according to claim 2, wherein said farnesyl transferase inhibitor is:

5-(2-(1-(4-cyanophenylmethyl)-imidazol-5-yl)-1-oxo-ethyl)-5,6-dihydro-2-phenyl-1H-imidazo[1,2-a][1,4]benzodiazepine;
or a pharmaceutically acceptable salt thereof.

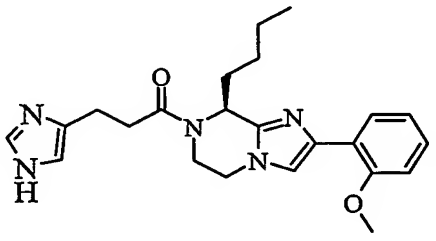
14. A combination according to claim 2, wherein said farnesyl transferase inhibitor is:

1,2-dihydro-1-(2-(imidazol-1-yl)-1-oxoethyl)-4-(2-methoxyphenyl) imidazo[1,2a][1,4]benzodiazepine;

1,2-dihydro-4-(2-methoxyphenyl)-1-(2-(pyridin-3-yl)-1-oxoethyl) imidazo[1,2a][1,4]benzodiazepine; or

1,2-dihydro-4-(2-methoxyphenyl)-1-(2-(pyridin-4-yl)-1-oxoethyl) imidazo[1,2a][1,4]benzodiazepine;
or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition according to claim 2, wherein said farnesyl transferase inhibitor is:



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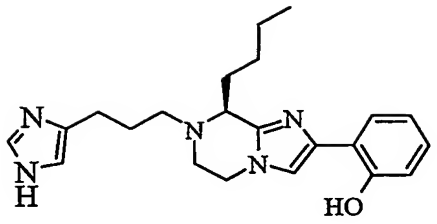
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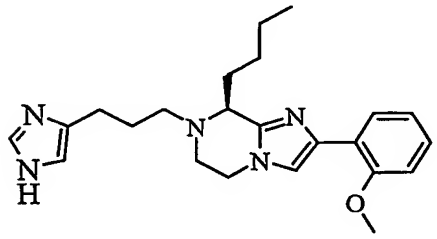
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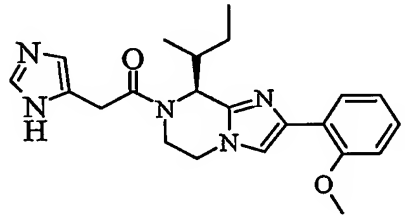
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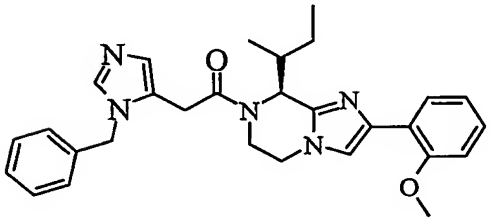
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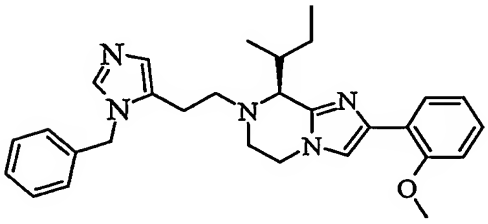
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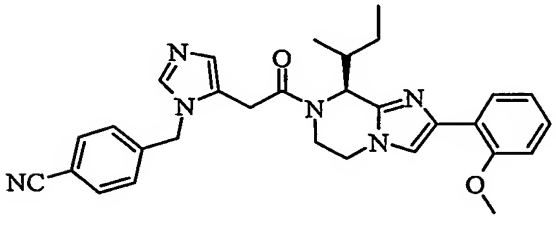
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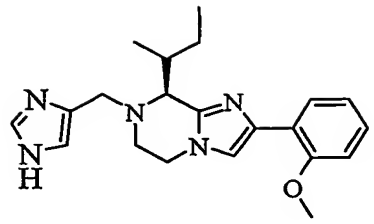
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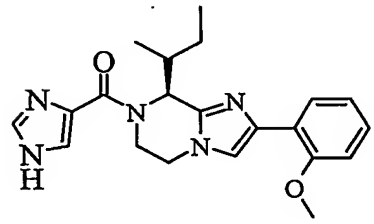
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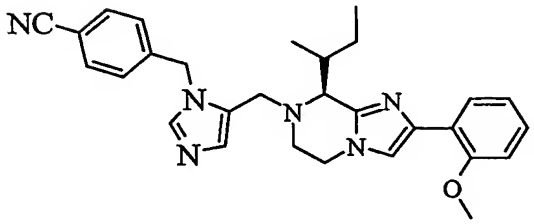
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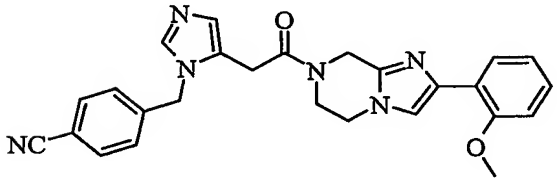
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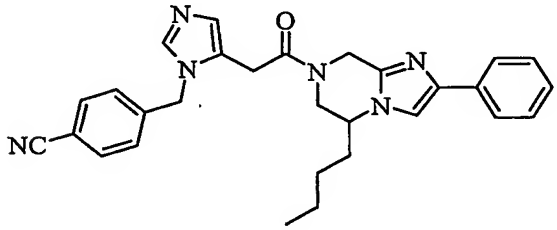
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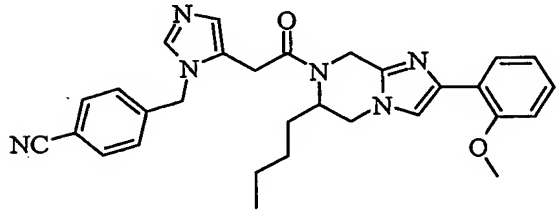
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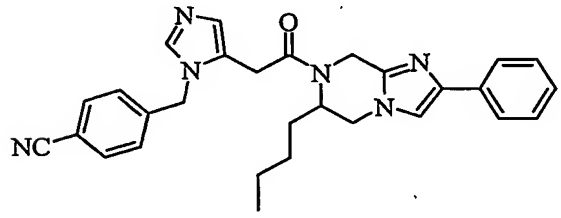
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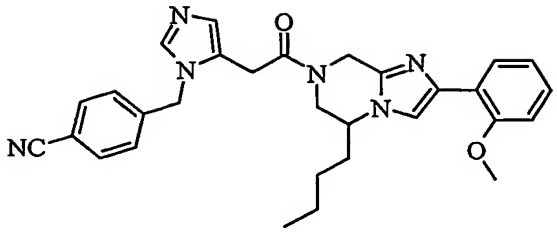

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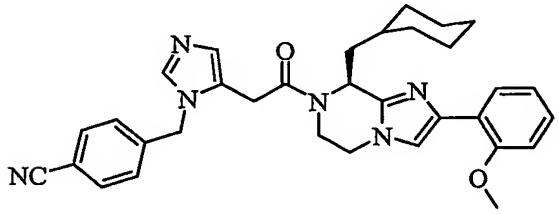

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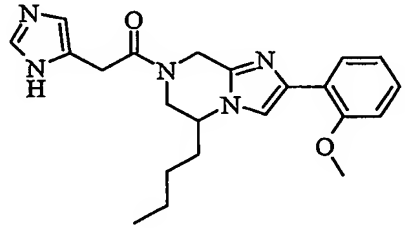

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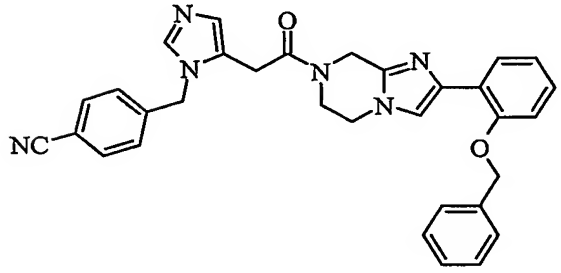

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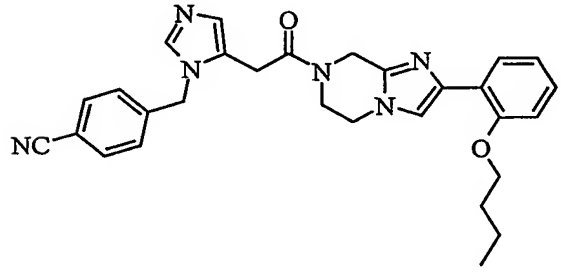

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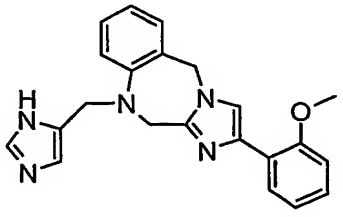

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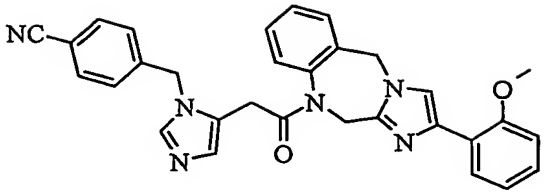
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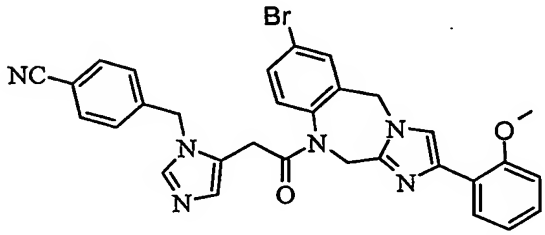
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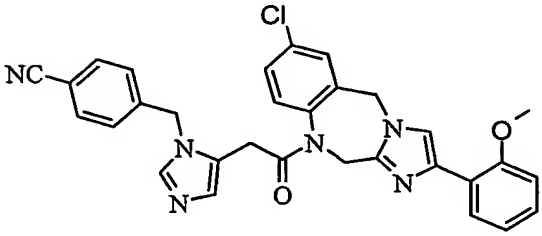
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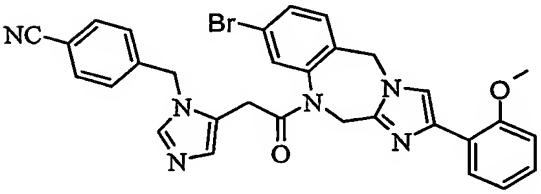
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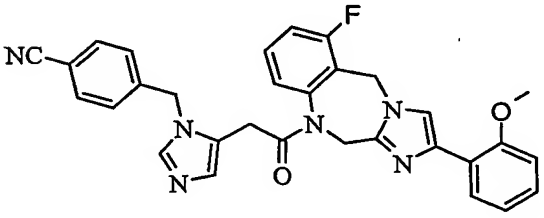
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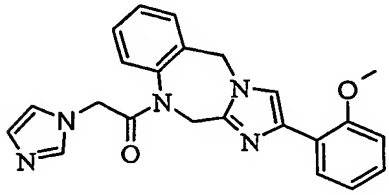
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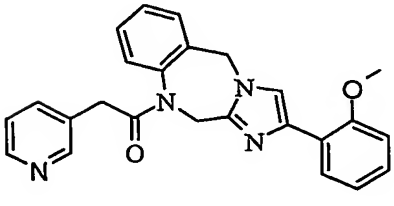
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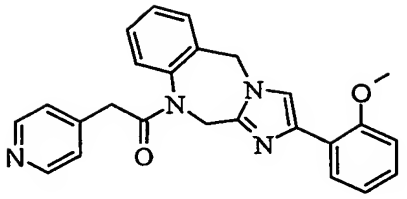
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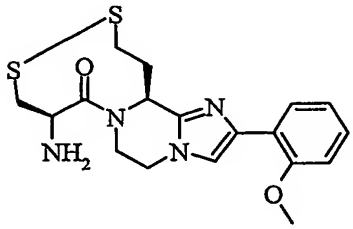
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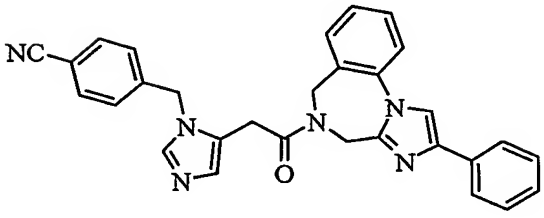
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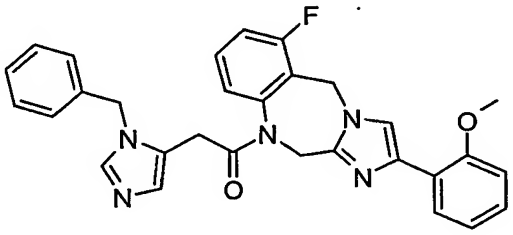
or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition according to claim 2, wherein said farnesyl transferase inhibitor is: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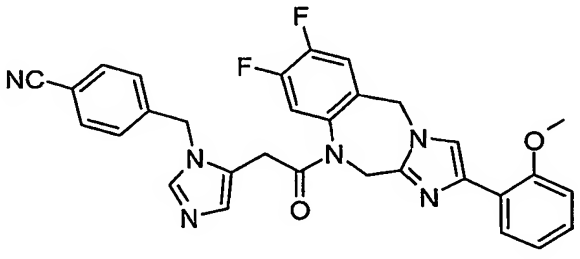
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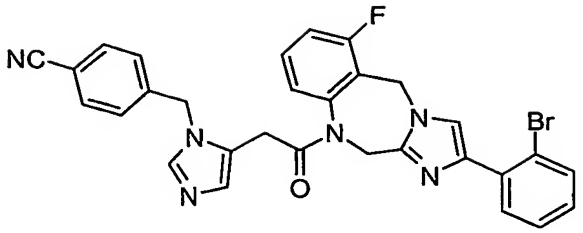
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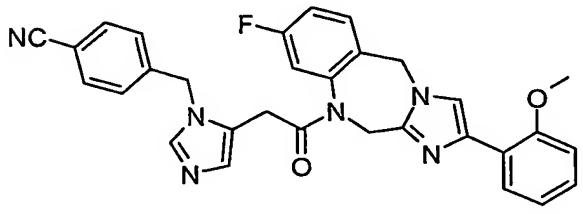
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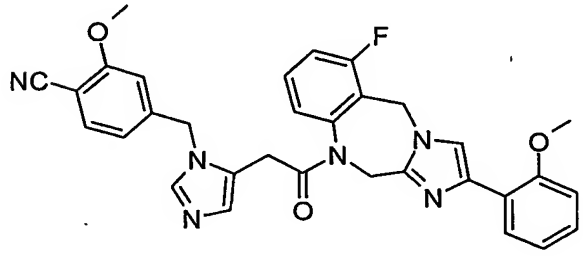
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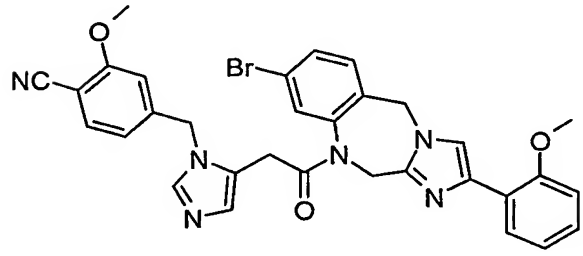
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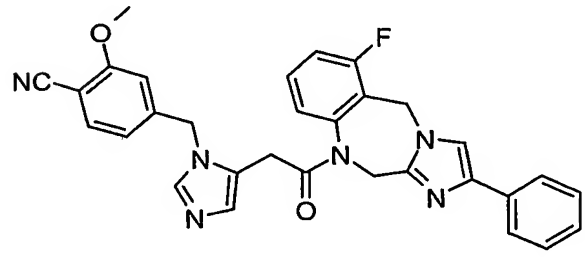
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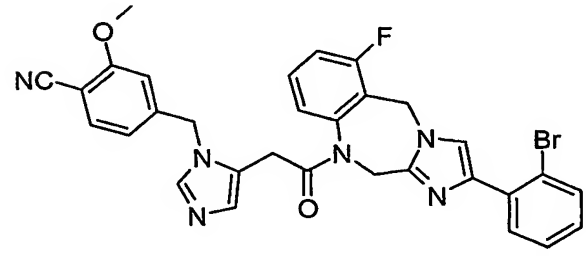
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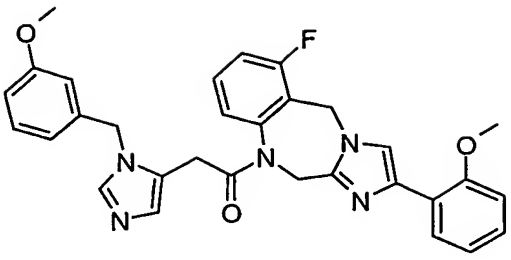

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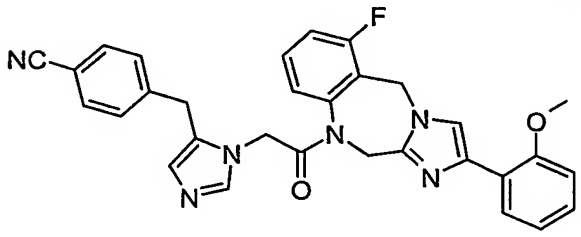
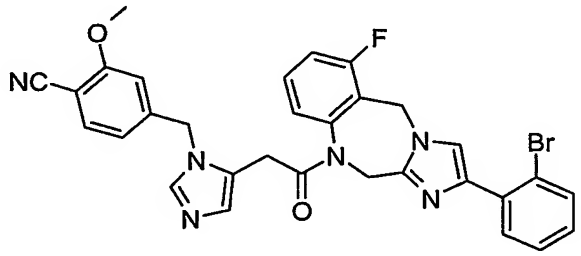


;

or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition according to claim 16, wherein said farnesyl transferase inhibitor is:



;

or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition according to claim 17, wherein said anthracyclin is doxorubicin, daunorubicin, epirubicin, idarubicin, or amrubicin, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition according to claim 17, wherein said anthracyclin is doxorubicin, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition according to any one of claims 1 - 17, wherein said anthracyclin is doxorubicin, daunorubicin, epirubicin, idarubicin, or amrubicin, or a prodrug thereof, or a pharmaceutically acceptable salt of said anthracyclin or of said anthracyclin prodrug.

21. A pharmaceutical composition according to claim 20, wherein said anthracyclin is doxorubicin, or a pharmaceutically acceptable salt thereof.

22. A method of decreasing the rate of proliferation of nasopharyngeal carcinoma cells, said method comprising contacting said nasopharyngeal cells with a pharmaceutical composition according to claim 18.

23. A method of decreasing the rate of proliferation of nasopharyngeal carcinoma cells, said method comprising contacting said nasopharyngeal cells with a pharmaceutical composition according to claim 19.

24. A method of decreasing the rate of proliferation of nasopharyngeal carcinoma cells, said method comprising contacting said nasopharyngeal cells with a pharmaceutical composition according to claim 20.

25. A method of decreasing the rate of proliferation of nasopharyngeal carcinoma cells, said method comprising contacting said nasopharyngeal cells with a pharmaceutical composition according to claim 21.

26. A method of treating nasopharyngeal carcinoma in a patient, said method comprising administering to said patient a pharmaceutical composition according to claim 18.

27. A method of treating nasopharyngeal carcinoma in a patient, said method comprising administering to said patient a pharmaceutical composition according to claim 19.

28. A method of treating nasopharyngeal carcinoma in a patient, said method comprising administering to said patient a pharmaceutical composition according to claim 20.

29. A method of treating nasopharyngeal carcinoma in a patient, said method comprising admini7stering to said patient a pharmaceutical composition according to claim 21.

30. A method of treating nasopharyngeal carcinoma in a patient, said method comprising administering to said patient an effective amount of one or more farnesyl transferase inhibiting compound in combination with an effective amount of one or more anthracycline compound, wherein said effective amount of said farnesyl transferase inhibiting compound or compounds and of said anthracycline compound or compounds are effective in combination to treat said nasopharyngeal carcinoma.

31. A method according to claim 30 wherein said patient is a mammal.

32. A method according to claim 31 wherein said patient is a human being.

33. A method according to claim 32 wherein said farnesyl transferase inhibiting compound and said anthracycline compound are administered substantially simultaneously.

34. A pharmaceutical kit comprising a composition according to claim 18 and instructions for use of said composition for the treatment of nasopharyngeal carcinoma.

35. A pharmaceutical kit comprising a composition according to claim 19 and instructions for use of said composition for the treatment of nasopharyngeal carcinoma.

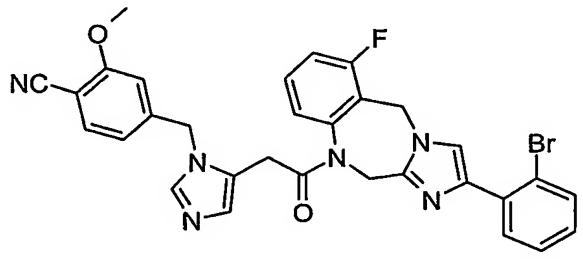
36. A pharmaceutical kit comprising a composition according to claim 20 and instructions for use of said composition for the treatment of nasopharyngeal carcinoma.

37. A pharmaceutical kit comprising a composition according to claim 21 and instructions for use of said composition for the treatment of nasopharyngeal carcinoma.

38. A kit comprising: a) a first unit dosage form comprising a farnesyl transferase inhibitor, a prodrug thereof or a pharmaceutically acceptable salt of said farnesyl transferase inhibitor or of said farnesyl transferase inhibitor prodrug and a pharmaceutically acceptable carrier, vehicle or diluent; b) a second unit dosage form comprising an anthracycline, a prodrug thereof or a pharmaceutically acceptable salt of said anthracycline or of said anthracycline prodrug and a pharmaceutically acceptable carrier, vehicle or diluent; and c) a container.

39. A kit according to claim 38, wherein said farnesyl transferase inhibitor comprises a compound according to formula I or a pharmaceutically acceptable salt thereof, and said anthracycline comprises doxorubicin, daunorubicin, epirubicin, idarubicin, or amrubicin or a pharmaceutically acceptable salt thereof.

40. A kit according to claim 39, wherein said farnesyl transferase inhibitor comprises a compound according to the formula:



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or a pharmaceutically acceptable salt thereof, and said anthracycline comprises doxorubicin or a pharmaceutically acceptable salt thereof.